Asymmetric Synthesis of 1-Substituted 1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazines

Andrea Gualandi, Lucia Cerisoli, Magda Monari, Diego Savoia*

Dipartimento di Chimica 'G. Ciamician', Università di Bologna, via Selmi 2, 40126 Bologna, Italy
Fax +39(051)2099456; E-mail: diego.savoia@unibo.it

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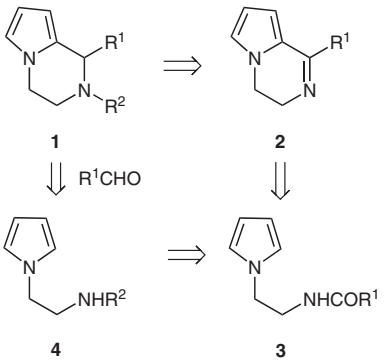
Abstract: The reactions of 1-(2-haloethyl)pyrrole-2-carbaldehydes with (1*S*)-1-phenylglycinol or (1*S*)-valinol gave the corresponding fused tricyclic oxazolidines as single diastereomers from which 1,2-disubstituted 1,2,3,4-tetrahydropyrrole[1,2-*a*]pyrazines were obtained by addition of organometallic reagents. The diastereoselectivity was dependent on the nature of both the chiral auxiliary and the organometallic reagent. The best diastereoselectivity (dr ≤ 98:2) was obtained by using Grignard reagents with the oxazolidine derived from (1*S*)-phenylglycinol. (+)-1-Methyl- and (+)-1-ethyl-1,2,3,4-tetrahydropyrrole[1,2-*a*]pyrazines were obtained by reductive removal of the N2-substituent.

Key words: asymmetric synthesis, diastereoselectivity, Grignard reagents, heterocycles, oxazolidines, tetrahydropyrrolopyrazines

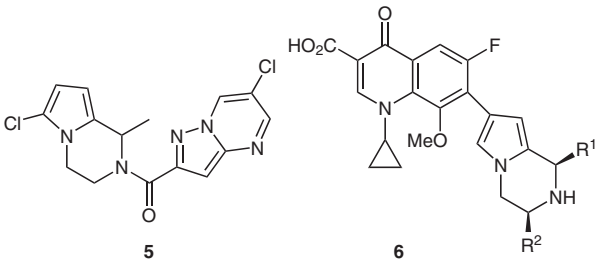
Substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines, e.g. **1** (Scheme 1), are extremely useful because of their antiamnesic, antihypoxic,[1] psychotropic,[2] and antihypersensitive[3] activities.[4] Moreover, a stereochemically defined 3,5,5-trisubstituted 2,4-dioxo derivative is a potent inhibitor of aldose reductase.[5] 1-Substituted and 1,2-disubstituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **1** have been synthesized by hydrogenation or reduction of 2-substituted 3,4-dihydropyrrolo[1,2-*a*]pyrazines **2**.[1,6–8] The dihydro compounds **2** are, in turn, prepared by reaction of 2-furylcarbaldehyde or 2-furyl ketones with ethylenediamine,[9–11] or by addition of Grignard reagents to unsubstituted **2** (R^1 = H).[12] Furthermore, hydrogenation of the pyrrole ring under more-forcing conditions has been used to obtain octahydro derivatives which are useful intermediates for the synthesis of coronary dilators and neuroleptics.[8] Dihydro compounds **2** have also been produced by phosphorus oxychloride-mediated condensation of *N*-[2-(pyrrol-1-yl)ethyl]carboxamides **3**, which are obtained, in turn, from 2,5-dimethoxytetrahydrofuran.[13,14] The N2-substituted derivatives **1** can be easily prepared from the N-unsubstituted precursors by routine alkylation/acylation reactions.[2,15] An alternative route to **1** involves the reaction of 1-(2-aminoethyl)pyrroles **4** with two equivalents of formaldehyde and benzotriazole, followed by addition of a Grignard reagent that provided the R^1 substituent. Similarly, 5,6,9,10,11,11a-hexahydro-8*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazines **1** [$R^1R^2 = CH_2CH_2CH_2CH(R)$]



Scheme 1 Retrosynthetic pathways for substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **1**

have been synthesized by the benzotriazole method using glutaric dialdehyde.[16]

The same skeleton is present in compounds **5** and **6** (Figure 1). The former, which is a modulator for human metabotropic glutamate receptor 5 (mGluR5), is useful in the control and prevention of chronic neurological disorders.[17] 7-(1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl)quinolones **6** have shown efficacy in vivo in a murine lethal systemic infection model; this efficacy is dependent on the position of the methyl group (R^2) at C3 of the tetrahydropyrazine ring and its *S*-configuration. In this case, the 1,2,3,4-tetrahydropyrazine fragment was constructed stereoselectively starting from (4*R*)-hydroxy-L-proline, and the pyrrole ring was obtained by dehydrogenation of an intermediate pyrroline.[18]



a: $R^1 = R^2$ = H
b: R^1 = H; R^2 = Me
c: R^1 = H; R^2 = (*R*)-Me
d: R^1 = Me; R^2 = H
e: R^1 = (*S*)-Me; R^2 = H
f: $R^1 = R^2$ = Me

Figure 1 Drugs containing substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine fragments

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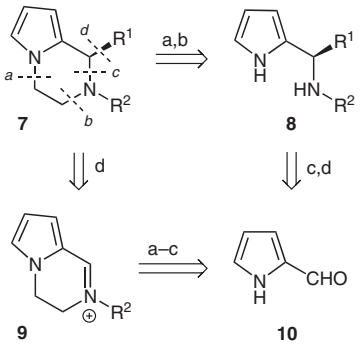
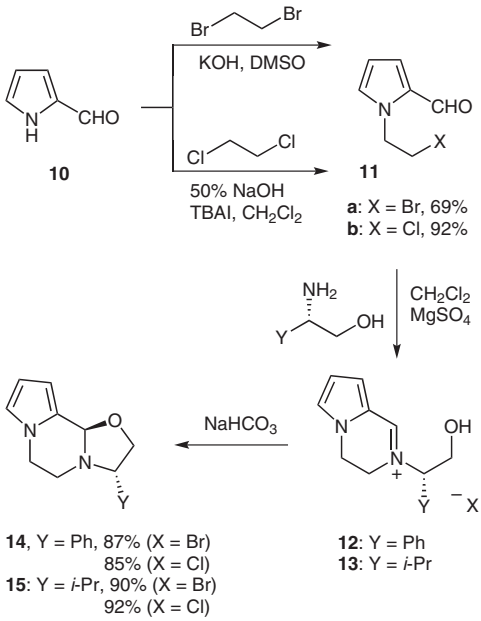
Because of the potential value of configurationally pure 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines, and taking into account our experience in the stereoselective synthesis of 1-(pyrrol-2-yl)alkylamines,[19] we decided to develop an efficient asymmetric route to the target compound **7** (Scheme 2). Two retrosynthetic pathways were envisaged, both involving the use of 2-pyrrolecarbaldehyde (**10**) as a convenient starting material an an optically pure primary amine as a chiral auxiliary. The two routes differ in the sequence in which the three C–N bonds (*a*–*c*) and one C–C bond (*d*) are formed, and they therefore involve 1-(2-pyrrolyl)alkylamines **8** or cyclic iminium ions **9** as intermediates.[20] In both cases, the chiral auxiliary, i.e. the nitrogen substituent R*, induces asymmetry during the formation of the new stereocenter. Finally, removal of the chiral auxiliary from **7** should lead to the desired N-unsubstituted 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines in an enantiomerically pure or enantiomerically enriched form.



Scheme 2 Retrosynthetic pathways for chiral 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **7**

We have previously reported a highly diastereoselective synthesis of N-substituted 1-(2-pyrrolyl)alkylamines **8** from aldehyde **10** through formation of an imine with (1*S*)-phenylglycinol, followed by the addition of an organolithium reagent (paths *c* and *d*).[19a] The products were converted into the corresponding primary amines by removal of the chiral auxiliary. To obtain the desired compounds **7** from **8**, the formation of two C–N bonds would be required (paths *a* and *b*). However, in a preliminary attempt to perform this transformation, the insertion of the two-carbon tether between the two nitrogen atoms of 1-(pyrrole-2-yl)-3-butenamine **8** (R = allyl; R* = H) by reaction with 1,2-dibromoethane by heating with sodium hydride in tetrahydrofuran failed. It is possible that this goal could be reached by an appropriate choice of the two-carbon 1,2-dielectrophilic reactant, e.g. chloroacetyl chloride, in a three-step sequence.[21] However, we reasoned that the alternative route described in Scheme 2 (sequence: *a*, *b*, *c*, *d*) offers several advantages, The first is that the electron-withdrawing effect of the formyl function results in an increased acidity of the pyrrole N–H bond in aldehyde **10**, facilitating metalation of the pyrrole and the formation of the first C–N bond by reaction with a 1,2-dihaloethane (step *a*). The second advantage is that ring-closure to the iminium ion **9** by subsequent reaction with an optically pure primary amine should occur in a single step by consecutive formation of two C–N bonds (*b* and *c* or *c* and *b*). The third and final advantage is that the enhanced reactivity of the iminium ion in comparison with an imine should permit the use of more-convenient Grignard reagents.

We therefore began our investigation by looking for optimal conditions for the conversion of aldehyde **10** into *N*-(2-haloethyl) derivatives **11a** and **11b** (Scheme 3). Treatment with potassium hydroxide in dimethyl sulfoxide at 0 °C for one hour followed by slow addition of 1,2-dibromoethane (20 equivalents)[22] and stirring for twenty-four hours resulted in a good conversion to **11a**; this was accompanied by small amounts of the corresponding *N*-vinyl derivative. After purification by column chromatography, the desired **11a** was isolated in 69% yield, but this compound decomposed slowly when stored at room temperature. To suppress this decomposition, the product was stored at 4 °C. On the other hand, when aldehyde **10** and 1,2-dichloroethane were stirred overnight in a two-phase system of 50% aqueous sodium hydroxide and dichloromethane in the presence of the tetrabutylammonium iodide as a phase-transfer catalyst, the air-stable *N*-(2-chloroethyl) derivative **11b** was obtained cleanly in 92% yield.[23]



Scheme 3 Diastereoselective synthesis of tricyclic oxazolidines **14** and **15** from 1*H*-pyrrole-2-carbaldehyde

Both halo aldehydes were treated with a slight excess of (1*S*)-phenylglycinol or (*S*)-valinol in anhydrous dichloromethane in the presence of anhydrous magnesium sulfate as a dehydrating agent for two days. In all cases, the corresponding bicyclic iminium ions **12** (Scheme 3) were observed in the crude products isolated by filtration of the solid and evaporation of the solvent. The ^{1}H NMR spectra of **12** in $CDCl_3$ showed an adsorption for the H–C=N$^+$

proton at δ = 9.33 ppm that was distinctly higher than that of the proton of the formyl group in **11a** (δ = 9.49 ppm). Minor amounts of starting material and another aldehyde, possibly 1-vinyl-2-pyrrolecarbaldehyde, were also detected. Moreover, an equilibrium was slowly established between the iminium **12** and the corresponding oxazolidine, and the chemical shift of the O–CH–N proton was observed at δ = 5.24 ppm. In practice, the crude iminium bromide **12** precipitated from its dichloromethane solution upon addition of diethyl ether and was obtained in 70% yield. However, this result could not be always reproduced when the same procedure was repeated. On the other hand, treatment of the dichloromethane solution with saturated aqueous sodium bicarbonate and extraction of the organic phase gave the pure tricyclic oxazolidine **14** in 87% yield. This last procedure was therefore used to prepare the tricyclic compound **15a** and **15b** from the corresponding halides **11a** and **11b** via the intermediate iminium ion **13**.[24]

The ^{1}H NMR spectra of the tricyclic structures **14** and **15** showed absorptions for the O–CH–N protons of the oxazolidine groups as singlets at δ = 5.58 and 5.24, respectively. At room temperature, minor amounts (about 5%) of another diastereoisomer could be observed, with some difficulty, in the spectrum, but the relevant signals became narrower and more evident at lower temperatures. The structure of **14** in the solid state (Figure 2) was confirmed by means of single-crystal X-ray diffraction studies on crystals grown by slow evaporation of a tetrahydrofuran solution of **14**.[25] This structure was found to corresponds to that of the most stable of the possible diastereomers (in which the N atom is also a stereocenter), as calculated at the MM2 level.

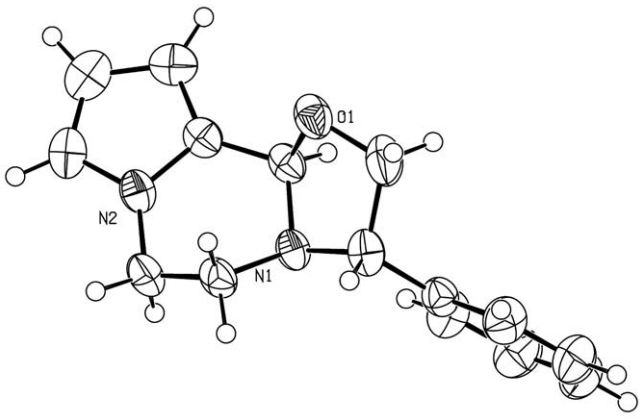


Figure 2 ORTEP drawing of compound **14**; thermal ellipsoids are at 30% probability

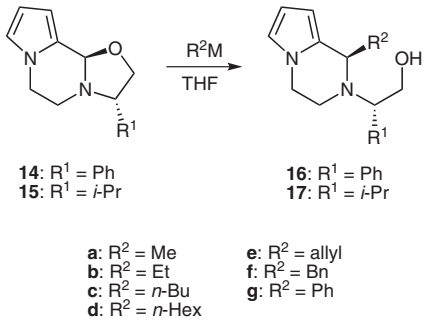
The tricyclic oxazolidines **14** and **15** were used as substrates for reactions with organometallic reagents.[26] Reactions of phenylglycinol-derived N-substituted oxazolidines with organometallic reagents have been previously used in the diastereoselective syntheses of secondary amines.[27,28] In our hands, Grignard reagents proved to be the reagents of choice for the reactions of **14**, giving, in many cases, high yields and high diastereoselectivities of 1,2-disubstituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **16** (Scheme 4 and Table 1).

The addition of methylmagnesium bromide in tetrahydrofuran at –78 °C was particularly effective in terms of both the yield and diastereoselectivity; the major diastereomer **16a** (dr 98:2) was obtained in a pure form and 95% yield after column chromatography (entry 1). The stereocontrol progressively decreased on increasing the length of the

Table 1 Addition of Organometallic Reagents to the Tricyclic Oxazolidine **14**

Entry[a]	RM	Temp (°C)	Time (h)	dr[b]	Product(s) [Yield (%)][c]
1	MeMgBr	–78	2	98:2	**16a** (95)
2	EtMgBr	–78	1	92:8	**16b** (78) + *epi*-**16b** (3)
3	$Me(CH_2)_5MgBr$	–78	1	93:7	**16d** (77) + *epi*-**16d** (6)
4	CH_2=$CHCH_2MgCl$	–78	1	50:50	**16e** (41) + *epi*-**16e** (35)
5	CH_2=$CHMgCl/TiCl_4$	–78	2[d]	–	–
6	CH_2=CHZnBr	–78 to 20	4	62:38	**16e** (47) + *epi*-**16e** (24)
7	CH_2=$CHZn(Et_2)MgCl$[e]	–781	1	76:24	**16e** (38) + *epi*-**16e** (14)
8	BnMgCl	–78	1	65:35	**16f** (53) + *epi*-**16f** (29)
9	PhMgBr	–78	1	>98:2	[**16g** + *epi*-**16g**] (72)[f]
10	PhLi	–78 to 20	1	78:22	[**16g** + *epi*-**16g**] (45)[f]

[a] The reactions were performed by adding the organometallic reagents (4 equiv) to a soln of the imine in anhyd THF under N_2.
[b] The diastereomeric ratios (dr) were determined by ^{1}H NMR analyses of the crude reaction product.
[c] Yields refer to pure diastereoisomers isolated by column chromatography (SiO_2).
[d] No reaction occurred.
[e] The zincate was prepared by adding allylmagnesium chloride to Et_2Zn in THF and stirring for 1 h at 0 °C.
[f] Pure diastereoisomers could not be obtained because epimerization occurred during chromatography on the SiO_2 column.



Scheme 4 Addition of organometallic reagents to the tricyclic oxazolidines **14** and **15**

alkyl group in the Grignard reagents (entries 2 and 3). Allylmagnesium chloride showed no stereoselectivity (entry 4) and gave no reaction in the presence of titanium tetrachloride (entry 5). We therefore examined the reaction of allylzinc bromide; however, the diastereoselectivity increased only slightly (entry 6). Better stereocontrol (dr 76:24) was achieved by using a preformed mixed zincate (entry 7). Benzylmagnesium chloride gave only a moderate diastereoselectivity (dr 65:35; entry 8). Finally, phenylmagnesium bromide reacted with almost complete stereocontrol to give a high yield of the crude secondary amine with a better than 99:1 dr (entry 9), whereas phenyllithium reacted sluggishly even when the temperature was increased to 20 °C (entry 10). Unfortunately, attempts to purify the crude phenyl-substituted product **16g** (entry 9) by chromatography on a silica-gel column resulted in epimerized product in all the eluted fractions. This can be explained by the acidity present in the silica inducing heterolytic cleavage of the benzydrylic C–N bond to form a carbenium ion that is stabilized by both adjacent aromatic rings.

Next, we examined the effectiveness of (*S*)-valinol as a chiral auxiliary by performing the same organometallic reactions on the oxazolidine **15** (Scheme 4 and Table 2). In all cases, we obtained unsatisfactory stereochemical outcomes, and the diastereomeric ratios ranged from 70:30 to 50:50 when Grignard reagents or butyllithium were used. Allyl(tributyl)stannane/tin tetrachloride and –boron trifluoride systems were totally unreactive, whereas the allyltitanium reagent formed in situ from the Grignard reagent and titanium tetraethoxide afforded **15e** with a lower yield than that obtained with the Grignard reagent alone, and the dr remained unsatisfactory. Moreover, column chromatography did not provide adequate separation of the diastereoisomers of the products **17b**,**e**–**g**. In particular, the phenyl-substituted product **17g**, initially obtained with a dr of 65:35, was eluted with an inverted dr of 40:60.

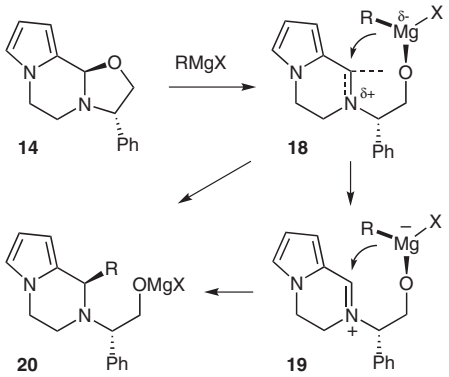
The absolute stereochemistry of the main diastereoisomers could not be unambiguously demonstrated; however, an *R*-configuration can reasonably be postulated by analogy with all the previously reported outcomes of Grignard reactions performed on various N-substituted oxazolidines derived from (*S*)-phenylglycinol.[25] We assume that the same mechanism considered for those reactions also operates with our substrate **14**, as shown in Scheme 5. The Lewis acidity of the Grignard reagent is a determinant for a successful reaction, which therefore proceeds by preliminary O–Mg coordination. This leads to the formation of the incipient carbenium ion **18** that undergoes attack of the R nucleophile from the side of the C–O bond being broken. In this way, adduct **20** is formed with an *R*-configuration at the newly formed stereocenter. The formation of a true carbenium ion **19** cannot be excluded and, in this case, a reduced diastereoselectivity might be expected owing to the possible rotation of the nitrogen substituent around the C*–N bond. Moreover, the

Table 2 Addition of Organometallic Reagents to the Tricyclic Oxazolidine **15**

Entry[a]	RM	Temp (°C)	Time (h)	dr[b]	Product(s) [Yields (%)][c]
1	MeMgBr	–78	2	70:30	**17a** (49) + *epi*-**17a** (17)
2	EtMgBr	–78	1	65:35	[**17b** + *epi*-**17b**] (68)[d]
3	BuLi	–78	1	70:30[e]	**17c**[f]
4	CH_2=$CHCH_2MgCl$	–78	1	50:50	[**17e** + *epi*-**17e**] (64)[d]
5	CH_2=$CHCH_2MgCl/Ti(OEt)_4$	–78	1	54:46	[**17e** + *epi*-**17e**] (50)[d]
6	CH_2=$CHCH_2SnBu_3/SnCl_4$	–78 to 20	4	–[f]	–
7	CH_2=$CHCH_2SnBu_3/BF_3$	–78 to 20	4	–[f]	–
8	BnMgCl	–78	1	50:50	[**17f** + *epi*-**17f**] (76)[d]
9	PhMgBr	–78	1	65:35	[**17g** + *epi*-**17g**] (78)[d]

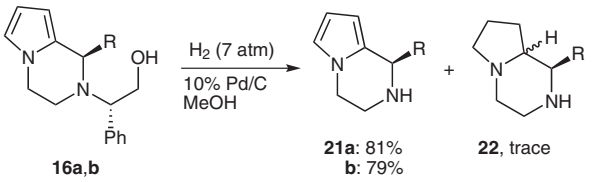
[a] The reactions were performed by adding the organometallic reagents (4 equiv) to a soln of the imine in anhyd THF under argon.
[b] The diastereomeric ratios (dr) were determined by ^{1}H NMR analysis of the crude reaction product.
[c] Yields refer to pure diastereoisomers isolated by column chromatography (SiO_2).
[d] The diastereomers could not be separated by column chromatography.
[e] No reaction occurred.
[f] The reaction mixture contained mainly unreacted **15** and minor amount of the addition product **17c** (~10%).
[g] The product was not isolated.

lower diastereoselectivity of allylic reagents can be explained in terms of an unfavorable transition state for the γ-attack.



Scheme 5 Mechanism and stereochemical model for the organometallic addition to oxazolidine **14**

Finally, we directed our efforts to the removal of the chiral auxiliary. Unfortunately, all efforts to achieve this goal by oxidative reactions of the amine **16** or amine **17**, including the use of periodic acid/methylamine and lead tetraacetate, were unsuccessful. Furthermore, hydrogenolysis of **16b** with ammonium formate and palladium/carbon gave a complex mixture of products. Finally, when **16a** or **16b** was subjected to 7 bar of hydrogen pressure in the presence of 10% palladium/carbon in methanol for two days, the desired secondary amines **21a** and **21b**, respectively, were obtained in about 80% yield together with 2-phenylethanol and trace amounts of the corresponding fully hydrogenated compounds **22** (Scheme 6).



Scheme 6 Removal of the chiral auxiliary from 1,2-disubstituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **16a**,**b**

In conclusion, we have developed the first asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines by a four-step route starting from 1*H*-pyrrole-2-carbaldehyde. The key intermediate, a tricyclic oxazolopyrrolopyrazine, was formed efficiently and diastereoselectively by condensation of a 1-(2-haloethyl)-2-pyrrolecarbaldehyde with (1*S*)-phenylglycinol. This intermediate reacted with Grignard reagents to give 1,2-disubstituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines with variable levels of diastereoselectivity that decreased with increasing the length of the alkyl group in the Grignard reagent. The highest diastereomeric ratios were obtained with methylmagnesium bromide (98:2) and phenylmagnesium bromide (>98:2). In the latter case, the product could not be purified by chromatography on silica gel because considerable epimerization occurred. The chiral auxiliary was removed from 1-methyl- and 1-ethyl-substituted products by hydrogenolysis to give the corresponding unsubstituted cyclic amines with a presumed *R*-configuration at the C1 stereocenter.

Melting points are uncorrected. Optical rotations were measured on a digital polarimeter in a 1-dm cell, and $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^3 g^{-1}. ^{1}H NMR spectra were recorded on Varian MR400 and Gemini 200 instruments for samples in $CDCl_3$ which was stored over Mg. The ^{1}H chemical shifts are reported in ppm relative to $CHCl_3$ (δ_H = 7.27) and the *J*-values are given in Hz. IR spectra were recorded on a Nicolet FT-380 spectrometer, and IR assignments are reported in wave numbers (cm^{-1}). MS spectra were recorded at an ionizing voltage of 70 eV on a Hewlett-Packard 5975 spectrometer with GC injection from a HP-5 column (30 m; ID 0.25 mm). Molecular weights were determined on an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck; 230–400 mesh) at medium pressure. All the organic, inorganic, and organometallic reagents and anhydrous solvents were purchased from Aldrich.

1-(2-Bromoethyl)-1*H*-pyrrole-2-carbaldehyde (11a)

KOH (5.88 g, 100 mmol) was added in one portion to a stirred soln of 1*H*-pyrrole-2-carbaldehyde (**10**; 1.00 g, 10 mmol) in anhyd DMSO (6 mL) at r.t. After 1 h, $Br(CH_2)_2Br$ (18.1 mL, 0.2 mol) was slowly added at 0 °C and the resulting soln was stirred overnight at r.t. The reaction was quenched by addition of H_2O (10 mL), and the organic layer was extracted with EtOAc (3 × 20 mL). The collected organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give a crude product that was purified by flash column chromatography [SiO_2, cyclohexane–EtOAc (9:1)] to give a yellow oil; yield: 1.59 g (75%).

IR (neat): 3111, 2947, 2807, 2722, 1660, 1530, 1479, 1321, 1208, 1075, 822, 623, 607 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 7.04–6.99 (m, 2 H), 6.29–6.25 (m, 1 H), 4.80 (t, *J* = 5.8 Hz, *J* = 6.2 Hz, 2 H), 3.70 (t, *J* = 5.8 Hz, *J* = 6.2 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.4, 150.9, 132.5, 125.6, 109.6, 50.6, 31.7.

MS (EI): *m/z* = 122 (100), 94 (36), 201 (14), 203 (12), 202 (3).

Anal. Calcd for C_7H_8BrNO (202.05): C, 41.61; H, 3.99; N, 6.93. Found: C, 41.50; H, 4.01; N, 6.91.

1-(2-Chloroethyl)-1*H*-pyrrole-2-carbaldehyde (11b)[23]

1,2-Dichloroethane (9.7 mL, 0.12 mol), Bu_4NI (1.94 g, 5.3 mmol), and 50% aq NaOH (5 mL) were added to a soln of 1*H*-pyrrole-2-carbaldehyde (**10**; 0.500 g, 5.3 mmol) in CH_2Cl_2 (2 mL), and the mixture was vigorously stirred overnight. H_2O (2 mL) was added and the organic layers were extracted with CH_2Cl_2 (2 × 30 mL) and washed with 1 M HCl (2 × 20 mL), sat. aq $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL). After drying (Na_2SO_4), the organic layers were concentrated in vacuo to give an orange slurry that was purified by column chromatography [SiO_2, cyclohexane–EtOAc (9:1)] to give a yellow oil; yield: 0.76 g (92%).

IR (neat) 3111, 2959, 2809, 1663, 1655, 1479, 882, 766, 705, 678, 656, 608 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.51 (s, 1 H), 7.03–6.97 (m, 2 H), 6.23 (t, *J* = 2.6 Hz, 1 H), 4.57 (t, *J* = 5.8 Hz, *J* = 5.4 Hz, 2 H), 3.79 (t, *J* = 5.8 Hz, *J* = 5.4 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.2, 132.7, 130.7, 125.4, 109.5, 50.5, 43.7.

MS (EI): *m/z* = 122 (100), 94 (50), 157 (34), 53 (19), 108 (18), 80 (14).

Anal. Calcd for C_7H_8ClNO (157.6): C, 53.35; H, 5.12; N, 8.89. Found: C, 53.19; H, 5.14; N, 8.86.

2-[(1*S*)-2-Hydroxy-1-phenylethyl]-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2-ium bromide (12)

A mixture of carbaldehyde **11a** (0.203 g, 1.0 mmol), (1*S*)-phenylglycinol (0.138 g, 1.2 mmol), and $MgSO_4$ (0.5 g) in anhyd CH_2Cl_2 (4 mL) was protected from light and magnetically stirred for 2 d under an inert atmosphere. The mixture was then filtered through a small pad of Celite that was washed with CH_2Cl_2. The filtered soln was concentrated under reduced pressure to a final volume of 1 mL, and Et_2O (3 mL) was slowly added to give a brown precipitate; yield: 0.228 g (71%).

IR (neat): 3381, 2962, 2924, 2848, 1646, 1629, 1491, 1377, 1103, 1067 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 7.39–7.26 (m, 7 H), 6.44–6.36 (m, 1 H), 5.56–5.49 (m, 1 H), 5.39 (br s, 1 H), 4.60–4.20 (m, 3 H), 4.10–3.93 (m, 2 H), 3.80–3.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 134.5, 132.7, 129.5, 127.9, 127.3, 122.6, 115.4, 72.5, 60.1, 45.9, 43.4.

MS (ES): *m/z* = 241.1 $[M - HBr + H]^+$ (100).

(3*S*,10b*R*)-3-Phenyl-2,3,5,6-tetrahydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (14); Typical Procedure

A mixture of carbaldehyde **11a** (1.515 g, 7.5 mmol), (1*S*)-phenylglycinol (1.233 g, 9.0 mmol), and $MgSO_4$ (5 g) in anhyd CH_2Cl_2 (15 mL) was protected from light and stirred for 2 d under an inert atmosphere. The mixture was then filtered through a small pad of Celite that was washed with CH_2Cl_2. The collected organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), and the organic phase was concentrated under reduced pressure to give a white solid; yield: 1.531 g (85%); mp 85.1–85.5 °C; $[\alpha]_D^{20}$ +8.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 3101, 3027, 2847, 1600, 1449, 1212, 1190, 873, 798, 757, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.34 (m, 5 H), 6.63 (dd, *J* = 1.6 Hz, *J* = 2.8 Hz, 1 H), 6.28 (d, *J* = 2.2 Hz, 1 H), 6.20 (t, *J* = 3.0 Hz, 1 H), 5.53 (s, 1 H), 4.50 (t, *J* = 7.9 Hz, 1 H), 4.30 (t, *J* = 6.8 Hz, 1 H), 4.14–4.03 (m, 2 H), 3.76 (dd, *J* = 6.6 Hz, *J* = 8.5 Hz, 1 H), 3.37–3.27 (m, 1 H), 3.16–3.07 (m, 1 H).

^{13}C NMR(100 MHz, $CDCl_3$): δ = 141.4, 134.9, 128.7, 127.3, 126.5, 119.5, 108.7, 107.6, 86.6, 71.2, 67.8, 47.4, 44.1.

MS (EI): *m/z* = 239 (100), 210 (20), 106 (15).

Anal. Calcd for $C_{15}H_{16}N_2O$ (240.30): C, 74.97; H, 6.71; N, 11.66. Found: C, 74.78; H, 6.74; N, 11.62.

(3*S*,10b*R*)-3-Isopropyl-2,3,5,6-tetrahydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazine (15)

This was prepared by the same procedure as **14**, starting from **11a** (1.515 g, 7.5 mmol).

Yellow oil; yield: 1.443 g (92%). $[\alpha]_D^{20}$ –13.0 (*c* 1.2, $CHCl_3$).

IR (neat): 3101, 2957, 2868, 1663, 1494, 1469, 1299, 1195, 1037, 861, 769, 609 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1 H), 6.28–6.24 (m, 1 H), 6.19 (t, *J* = 2.9 Hz, 1 H), 5.24 (s, 1 H), 4.14 (t, *J* = 8.0 Hz, 1 H), 4.06 (ddd, *J* = 3.5 Hz, *J* = 12.0 Hz, 1 H), 3.98–3.88 (m, 1 H), 3.50 (dd, *J* = 6.0 Hz, *J* = 8.1 Hz, 1 H), 3.21 (dt, *J* = 3.4 Hz, *J* = 11.5 Hz, 1 H), 2.86–2.78 (m, 1 H), 2.74–2.64 (m, 1 H), 1.74–1.64 (m, 1 H) 1.07 (d, *J* = 6.4 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 124.7, 119.2, 108.6, 107.5, 85.7, 72.7, 67.6, 48.7, 44.9, 31.9, 20.3, 18.9.

MS (EI): *m/z* = 205 (100), 161 (90), 176 (13).

Anal. Calcd for $C_{12}H_{18}N_2O$ (206.28): C, 69.87; H, 8.80; N, 13.58. Found: C, 69.60; H, 8. 83; N, 13.54.

(2*S*)-2-[(1*R*)-1-Methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-phenylethanol (16a); Typical Procedure

A 3.0 M soln of MeMgCl in Et_2O (1.3 mL, 4.0 mmol) was added to a magnetically stirred soln of tricycle **14** (0.240 g, 1.0 mmol) in anhyd THF (15 mL) at –78 °C, and the mixture was stirred until no starting material remained (TLC). The reaction then was quenched by adding sat. aq $NaHCO_3$ (10 mL), and the organic material was extracted with Et_2O (3 × 10 mL). The collected ethereal layers were dried (Na_2SO_4) and concentrated to give an oil. The diastereomeric ratio was determined by ^1H NMR analysis of a sample soln in $CDCl_3$. Flash column chromatography [SiO_2, cyclohexane–EtOAc (9:1)] gave a yellow oil; yield: 0.253 g (99%): $[\alpha]_D^{20}$ –21.4 (*c* 1.3, $CHCl_3$).

IR (neat): 3415, 3101, 3050, 2970, 2928, 1601, 1492, 1453, 1266, 1186, 1056, 735, 609 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.29 (m, 5 H), 6.50 (t, *J* = 1.7 Hz, 1 H), 6.15 (t, *J* = 3.0 Hz, 1 H), 5.85–5.80 (m, 1 H), 4.30 (q, *J* = 6.8 Hz, *J* = 13.0 Hz, 1 H), 4.02–3.90 (m, 3 H), 3.82–3.75 (m, 1 H), 3.43 (t, *J* = 6.7 Hz, 1 H), 3.38–3.21 (m, 1 H), 3.10–3.02 (m, 1 H), 1.39 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 132.1, 128.6, 128.4, 128, 3, 117.9, 107.8, 102.9, 65.4, 63.2, 50.8, 43.38, 41.3, 19.2.

MS (ES): *m/z* = 257.2 $[M + H]^+$ (100).

Anal. Calcd for $C_{16}H_{20}N_2O$ (256.34): C, 74.97; H, 7.86; N, 10.93. Found: C, 74.75; H, 7.88; N, 10.90.

(2*S*)-2-[(1*R*)-1-Ethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-phenylethanol (16b)

Yellowish oil; yield: 0.210 g (78%); $[\alpha]_D^{20}$ –10.5 (*c* 0.5, $CHCl_3$).

IR (neat): 3411, 3109, 3046, 2974, 2921, 1605, 1457, 1174, 1050, 736 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H), 6.52 (t, *J* = 1.8 Hz, 1 H), 6.12 (t, *J* = 3.2 Hz, 1 H), 5.79–6.75 (m, 1 H), 4.04 (dt, *J* = 4.6 Hz, *J* = 11.8 Hz, 1 H), 3.96–3.88 (m, 3 H), 3.82–3.73 (m, 2 H), 3.46–3.36 (m, 1 H), 3.22–3.14 (m, 1 H), 1.86–1.74 (m, 1 H), 1.71–1.58 (m, 1 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 130.0, 128.5, 127.7, 118.3, 107.4, 104.0, 65.2, 63.6, 56.4, 41.6, 40.9, 26.8, 11.0.

MS (ES): *m/z* = 271.2 $[M + H]^+$ (100).

Anal. Calcd for $C_{17}H_{22}N_2O$ (270.37): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.68; H, 8.21; N, 10.32.

***epi*-16b**

Yellowish oil; yield: 0.008 g (3%); $[\alpha]_D^{20}$ +6.8 (*c* 1.2, $CHCl_3$).

IR (neat): 3414, 3107, 3054, 2978, 2923, 1611, 1497, 1451, 1263, 1051, 736 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5 H), 6.47 (t, *J* = 1.8 Hz, 1 H), 6.12 (t, *J* = 2.9 Hz, 1 H), 5.85–5.81 (m, 1 H), 4.20 (dd, *J* = 5.2 Hz, *J* = 9.6 Hz, 1 H), 4.07 (dd, *J* = 10.4 Hz, 1 H), 3.98 (t, *J* = 4.2 Hz, 1 H), 3.96–3.84 (m, 2 H), 3.76 (dd, *J* = 4.9 Hz, *J* = 10.8 Hz, 1 H), 3.28–3.20(m, 1 H), 3.02 (br s, 1 H), 2.54–2.45 (m, 1 H), 2.21–2.14 (m, 1 H), 1.98–1.88 (m, 1 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3, 129.9, 129.0, 128.4, 118.1, 107.9, 103.5, 62.4, 60.7, 55.9, 44.3, 41.7, 25.6, 8.3.

MS (ES): *m/z* = 271.2 $[M + H]^+$ (100).

(2*S*)-2-[(1*R*)-1-Hexyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-phenylethanol (16d)
Light-brown oil; yield: 0.251 g (77%); $[\alpha]_D^{20}$ –5.9 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 6.52 (t, *J* = 2.2 Hz, 1 H), 6.11 (t, *J* = 3.2 Hz, 1 H), 5.78–5.76 (m, 1 H), 4.05 (dt, *J* = 4.7 Hz, *J* = 11.7 Hz, 1 H), 3.97–3.91 (m, 3 H), 3.80–3.74 (m, 1 H), 3.50–3.38 (m, 1 H), 3.21–3.16 (m, 1 H), 1.85–1.71 (m, 1 H), 1.70–1.55 (m, 1 H), 1.41–1.18 (m, 10 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 128.6, 128.4, 127.8, 118.3, 107.5, 104.0, 65.3, 63.8, 54.9, 41.4, 40.9, 34.1, 31.8, 29.2, 26.4, 22.6, 14.0.

MS (ES): *m/z* = 327.1 $[M + H]^+$ (100).

Anal. Calcd for $C_{21}H_{30}N_2O$ (326.48): C, 77.26; H, 9.26; N, 8.58. Found: C, 77.56; H, 9.29; N, 8.55.

***epi*-16d**
Yellow oil; yield: 0.020 g (6%); $[\alpha]_D^{20}$ +5.4 (*c* 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 5 H), 6.60 (t, *J* = 2.2 Hz, 1 H), 6.20 (t, *J* = 2.5 Hz, 1 H), 5.80–5.75 (m, 1 H), 4.36–4.26 (m, 1 H), 4.25–4.16 (m, 2 H), 3.72–3.66 (m, 1 H), 3.37–3.27 (m, 1 H), 3.15–3.08 (m, 1 H), 2.04–1.98 (m, 2 H), 1.40–1.18 (m, 10 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 131.3, 128.6, 127.8, 127.5, 118.6, 107.9, 104.9, 72.7 63.0, 42.2, 31.8, 30.1, 29.6, 29.4, 26.8, 23.6, 22.6, 14.1.

MS (ES): *m/z* = 327.1 $[M + H]^+$ (100).

(2*S*)-2-[(1*R*)-1-Allyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-phenylethanol (16e)
Light-brown oil; yield: 0.107 g (38%); $[\alpha]_D^{20}$ +18.3 (*c* 0.9, $CHCl_3$).

IR (neat): 3416, 3068, 2924, 2852, 1639, 1569, 1492, 1333, 1290, 1069, 1029, 914, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H), 6.52 (t, *J* = 1.7 Hz, 1 H), 6.11 (t, *J* = 2.9 Hz, 1 H), 5.88–5.80 (m, 1 H), 5.79–5.76 (m, 1 H), 5.09–4.99 (m, 2 H), 4.06 (t, *J* = 6.7 Hz, 1 H), 4.03–3.93 (m, 2 H), 3.92–3.87 (m, 2 H), 3.79–3.72 (m, 1 H), 3.46–3.38 (m, 1 H), 3.20–3.13 (m, 1 H), 2.63–2.52 (m, 1 H), 2.47–2.38 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 136.1, 129.5, 128.5, 128.4, 127.8, 118.4, 116.8, 107.5, 103.9, 65.7, 63.4, 54.6, 41.7, 41.6, 38.8.

MS (ES): *m/z* = 283.2 $[M + H]^+$ (100), 305.2 $[M + Na]^+$ (15).

Anal. Calcd for $C_{18}H_{22}N_2O$ (282.38): C, 76.56; H, 7.85; N, 9.92. Found: C, 76.58; H, 7.87; N, 9.90.

***epi*-16e**
Yellowish oil; yield: 0.039 g (14%); $[\alpha]_D^{20}$ –13.4 (*c* 0.8, $CHCl_3$).

IR (neat): 3415, 3078, 2975, 2926, 2849, 2793, 1639, 1496, 1485, 1339, 1219, 1119, 1002, 849, 704 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 5 H), 6.47 (t, *J* = 1.6 Hz, 1 H), 6.12 (t, *J* = 3.3 Hz, 1 H), 5.89–5.86 (m, 1 H), 5.80–5.67 (m, 1 H), 5.22 (s, 1 H), 5.14 (t, *J* = 11.6 Hz, 1 H), 4.22 (dd, *J* = 4.8 Hz, *J* = 9.7 Hz, 1 H), 4.13 (t, *J* = 4.1 Hz, 1 H), 4.05 (t, *J* = 10.6 Hz, 1 H), 3.94–3.87 (m, 2 H), 3.73 (dd, *J* = 4.8 Hz, *J* = 10.9 Hz, 1 H), 3.26–3.18 (m, 1 H), 2.94–2.85 (m, 1 H), 2.76–2.68 (m, 1 H), 2.55–2.47 (m, 1 H), 1.57 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 134.6, 128.9, 128.4, 128.2, 118.2, 117.7, 108.0, 103.8, 62.7, 60.6, 54.7, 44.2, 41.5, 38.3.

MS (ES): *m/z* = 283.2 $[M + H]^+$ (100), 305.1 $[M + Na]^+$ (23).

(2*S*)-2-[(1*R*)-1-Benzyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-phenylethanol (16f)
Yellowish oil; yield: 0.176 g (53%); $[\alpha]_D^{20}$ –86.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.03 (m, 10 H), 6.48 (dd, *J* = 1.7 Hz, *J* = 2.6 Hz, 1 H), 6.06 (t, *J* = 3.1 Hz, 1 H), 5.48 (dd, *J* = 1.4 Hz, *J* = 3.4 Hz, 1 H), 4.14 (t, *J* = 7.4 Hz, 1 H), 4.10–3.98 (m, 1 H), 3.90 (t, *J* = 5.1 Hz, 1 H), 3.79–3.70 (m, 2 H), 3.67–3.58 (m, 1 H), 3.36–3.24 (m, 2 H), 3.13 (dd, *J* = 7.9 Hz, *J* = 13.2 Hz, 1 H), 2.83 (dd, *J* = 6.3 Hz, *J* = 13.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 139.2, 131.2, 129.6, 129.1, 128.5, 128.4, 128.2, 128.1, 127.7, 127.6, 127.5, 126.2, 118.3, 107.4, 104.2, 66.1, 63.8, 56.3, 41.5, 41.3, 40.9.

MS (ES): *m/z* = 333.2 $[M + H]^+$ (100).

Anal. Calcd for $C_{22}H_{24}N_2O$ (332.44): C, 79.48; H, 7.28; N, 8.43. Found: C, 79.28; H, 7.31; N, 8.41.

***epi*-16f**
Yellowish oil; yield: 0.096 g (29%); $[\alpha]_D^{20}$ +14.3 (*c* 1.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.12 (m, 10 H), 6.46 (m, 1 H), 6.12 (t, *J* = 3.1 Hz, 1 H), 5.77 (m, 1 H), 4.38 (t, *J* = 6.4 Hz, 1 H), 4.04 (dd, *J* = 4.9 Hz, *J* = 7.1 Hz, 1 H), 3.75 (dd, *J* = 7.7 Hz, *J* = 11.0 Hz, 1 H), 3.71–3.54 (m, 3 H), 3.30–3.21 (m, 2 H), 3.10 (dd, *J* = 5.8 Hz, *J* = 13.2 Hz, 1 H), 2.75 (ddd, *J* = 4.2 Hz, *J* = 5.8 Hz, *J* = 13.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 137.2, 129.5, 128.7, 128.4, 128.3, 128.2, 128.0, 126.5, 118.2, 104.2, 64.4, 61.7, 56.7, 42.5, 41.9, 40.4.

MS (ES): *m/z* = 333.1 $[M + H]^+$ (100).

(2*S*)-2-Phenyl-2-[(1*R*/1*S*)-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]ethanol (16g + *epi*-16g)
Oil; yield: 0.141 g (45%); dr 60:40.

Representative signals for **16g** in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the mixture were observed at δ = 6.61 (dd, *J* = 2.0 Hz, *J* = 2.8 Hz, 1 H), 6.15 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.59 (m, 1 H), 5.06 (s, 1 H), 3.29 (m, 1 H), 3.21 (m, 1 H).

MS (ES): *m/z* = 319.1 $[M + H]^+$ (100).

Representative ^{1}H NMR signals for *epi*-**16g**: δ = 6.51 (t, *J* = 1.6 Hz, 1 H), 6.03 (t, *J* = 3.2 Hz, 1 H), 5.27 (m, 1 H), 4.79 (s, 1 H), 4.22 (dd, *J* = 4.6 Hz, *J* = 10.6 Hz, 1 H), 4.22 (ddd, *J* = 1.9 Hz, *J* = 3.0 Hz, *J* = 12.1 Hz, 1 H), 2.59 (ddd, *J* = 3.7 Hz, *J* = 12.1 Hz, *J* = 12.2 Hz, 1 H).

MS (ES): *m/z* = 319.1 $[M + H]^+$ (100).

Anal. Calcd for $C_{21}H_{22}N_2O$ (318.41): C, 79.21; H, 6.96; N, 8.80. Found: C, 79.02; H, 6.97; N, 8.78.

(2*S*)-3-Methyl-2-[(1*R*)-1-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]butan-1-ol (17a)
Yellowish oil; yield: 0.033 g (15%); $[\alpha]_D^{20}$ +23.4 (*c* 1.0, $CHCl_3$).

IR (neat): 3361, 2968, 2934, 2853, 1466, 1449, 1367, 1315, 1114, 1080, 1069, 1019, 886, 733, 715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56–6.53 (m, 1 H), 6.18 (t, *J* = 3.3 Hz, 1 H), 5.91–5.89 (m, 1 H), 4.34 (q, *J* = 6.2 Hz, *J* = 12.2 Hz, 1 H), 4.00–3.92 (m, 2 H), 3.62 (dd, *J* = 5 Hz, *J* = 10.2 Hz, 1 H), 3.31 (t, *J* = 10.6 Hz, 1 H), 3.19–3.12 (m, 1 H), 3.10–3.00 (m, 1 H), 2.99–2.90 (m, 1 H), 2.00–1.90 (m, 1 H), 1.47 (d, *J* = 6.4 Hz, 3 H), 1.08 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.5, 118.4, 108.0, 103.2, 63.1, 58.8, 53.0, 45.7, 41.4, 27.9, 22.6, 20.9, 19.9.

MS (EI): *m/z* = 207 (100), 121 (53), 191 (35), 222 (1).

MS (ES): *m/z* = 223.1 $[M + H]^+$ (100).

Anal. Calcd for $C_{13}H_{22}N_2O$ (222.33): C, 70.23; H, 9.97; N, 12.60. Found: C, 70.19; H, 10.00; N, 12.58.

***epi*-(17a)**
Yellow oil; yield: 0.011 g (5%); $[\alpha]_D^{20}$ –15.2 (*c* 1.0, $CHCl_3$).

IR (neat) 3407, 2954, 2921, 1581, 1450, 1348, 1066, 1029, 731, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.53–6.50 (m, 1 H), 6.15 (t, *J* = 3.0 Hz, 1 H), 5.88–5.84 (m, 1 H), 4.21 (q, *J* = 6.4 Hz, *J* = 12.7 Hz, 1 H), 4.00–3.86 (m, 2 H), 3.81 (dd, *J* = 3.7 Hz, *J* = 11.2 Hz, 1 H), 3.69 (dd, *J* = 7.1 Hz, *J* = 11.1 Hz, 1 H), 3.24–314 (m, 1 H), 2.68–2.60 (m, 1 H), 2.03–190 (m, 1 H), 2.00–1.90 (m, 1 H), 1.41 (d, *J* = 6.2 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.2 118.0, 107.8, 102.8, 66.2, 60.2, 52.2, 45.7, 44.9, 27.6, 21.7, 20.9, 20.1.

MS (EI): *m/z* = 207 (100), 121 (51), 191 (19), 222 (1).

MS (ES): *m/z* = 223.1 $[M + H]^+$ (100).

(2*S*)-2-[(1*R*/1*S*)-1-Ethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-methylbutan-1-ol (17b + *epi*-17b)
Yellow oil; yield: 0.160 g (68%); dr 65:35.

^1H NMR (400 MHz, $CDCl_3$): δ (representative signals for **17b**) = 4.23 (t, *J* = 4.6 Hz, 1 H), 3.64 (dd, *J* = 5.2 Hz, *J* = 10.4 Hz, 1 H), 3.35 (t, *J* = 10.4 Hz, 1 H), 3.04 (dt, *J* = 3.2 Hz, *J* = 11.7 Hz, 1 H), 2.77 (m, 1 H); δ (representative signals for *epi*-**17b**) = 4.08 (t, *J* = 4.7 Hz, 1 H), 3.82 (dd, *J* = 3.5 Hz, *J* = 11.4 Hz, 1 H), 3.69 (dd, *J* = 6.1 Hz, *J* = 6.8 Hz, 1 H), 3.20 (dt, *J* = 4.0 Hz, *J* = 12.3 Hz, 1 H), 2.50 (m, 1 H).

Anal. Calcd for $C_{14}N_{24}N_2$ (236.25): C, 71.14; H, 10.23; N, 11.85. Found: C, 71.11; H, 10.25; N, 11.84.

(2*S*)-2-[(1*R*/1*S*)-1-Allyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-methylbutan-1-ol (17e + *epi*-17e)
Yellowish oil; yield: 0.158 g (64%); dr 50:50.

^1H NMR (400 MHz, $CDCl_3$): δ (representative signals for **17e**) = 6.57–6.55 (m, 1 H), 5.95–5.88 (m, 1 H), 5.62–5.49 (m, 1 H), 4.39 (t, *J* = 4.2 Hz, 1 H), 4.23 (t, *J* = 5.1 Hz, 1 H), 3.36 (t, *J* = 10.4 Hz, 1 H), 3.09–2.93 (m, 2 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); δ (representative signals for *epi*-**17e**) = 6.54–6.50 (m, 1 H), 5.87–5.84 (m, 1 H), 5.83–5.71 (m, 1 H), 3.28 (dt, *J* = 4.6 Hz, *J* = 12.8 Hz, 1 H), 2.85–2.77 (m, 1 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

Anal. Calcd for $C_{15}H_{24}N_2$ (248.36): C, 72.54; H, 9.74; N, 11.28. Found: C, 72.28; H, 9.76; N, 11.24.

(2*S*)-2-[(1*R*/1*S*)-1-Benzyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-methylbutan-1-ol (17f + *epi*-17f)
Light-red oil; yield: 0.226 g (76%); dr 50:50.

^1H NMR (400 MHz, $CDCl_3$): δ (representative signals for **17f**) = 7.33–7.21 (m, 4 H), 6.95 (m, 1 H), 6.54 (m, 1 H), 6.11 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.64 (ddd, *J* = 0.7 Hz, *J* = 1.6 Hz, *J* = 3.5 Hz, 1 H), 4.54 (dd, *J* = 4.8 Hz, *J* = 6.1 Hz, 1 H), 3.86 (dt, *J* = 3.9 Hz, *J* = 12.1 Hz, 1 H), 3.64 (dd, *J* = 5.1 Hz, *J* = 10.7 Hz, 1 H), 3.54 (m, 1 H), 3.33 (t, *J* = 10.7 Hz, 1 H), 3.17 (dd, *J* = 4.6 Hz, *J* = 13.1 Hz, 1 H), 3.00–2.87 (m, 3 H), 2.82 (ddd, *J* = 5.1 Hz, *J* = 7.9 Hz, *J* = 13.1 Hz, 1 H), 1.87 (m, 1 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (representative signals for **17f**) = 138.3, 129.7, 128.5, 128.1, 126.3, 118.3, 107.4, 104.5, 66.8, 50.1, 44.9, 43.8, 43.0, 40.6, 28.4, 22.0, 19.7.

MS (ES): *m/z* = 299.2 $[M + H]^+$ (100).

^1H NMR (400 MHz, $CDCl_3$): δ (representative signals for *epi*-**17f**) = 4.34 (t, *J* = 6.7 Hz, 1 H), 3.93 (ddd, *J* = 4.3 Hz, *J* = 8.3 Hz, *J* = 12.3 Hz, 1 H), 3.78 (ddd, *J* = 4.3 Hz, *J* = 5.3 Hz, *J* = 12.3 Hz, 1 H), 3.44 (dd, *J* = 4.3 Hz, *J* = 8.3 Hz, *J* = 13.1 Hz, 1 H), 2.65 (t, *J* = 7.7 Hz, 1 H), 2.58 (ddd, *J* = 3.8 Hz, *J* = 6.3 Hz, *J* = 10.2 Hz, 1 H), 1.80 (m, 1 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H).

MS (ES): *m/z* = 299.2 $[M + H]^+$ (100).

Anal. Calcd for $C_{19}H_{26}N_2$ (298.42): C, 76.47; H, 8.78; N, 9.39. Found: C, 76.45; H, 8.78; N, 9.37.

(2*S*)-3-Methyl-2-[(1*R*/1*S*)-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]butan-1-ol (17g + *epi*-17g)
Light-red oil; yield: 0.221 g (78%); dr 40:60.

^1H NMR (400 MHz, $CDCl_3$): δ (representative signals for **17g**) = 7.36–7.28 (m, 5 H), 6.58 (m, 1 H), 6.08 (dd, *J* = 2.8 Hz, *J* = 3.5 Hz, 1 H), 5.32 (m, 1 H), 5.19 (s, 1 H), 4.15 (ddd, *J* = 4.0 Hz, *J* = 11.3 Hz, *J* = 11.4 Hz, 1 H), 4.08 (ddd, *J* = 2.1 Hz, *J* = 3.9 Hz, *J* = 11.4 Hz, 1 H), 3.42 (dd, *J* = 5.2 Hz, *J* = 10.7 Hz, 1 H), 3.35 (t, *J* = 10.7 Hz, 1 H), 3.29 (ddd, *J* = 1.9 Hz, *J* = 4.0 Hz, *J* = 12.1 Hz, 1 H), 3.16 (m, 1 H), 2.61 (ddd, *J* = 5.4 Hz, *J* = 6.4 Hz, *J* = 11.6 Hz, 1 H), 2.04 (m, 1 H), 1.05 (d, *J* = 6.4 Hz, 3 H), 0.83 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8, 131.8, 129.4, 128.6, 128.0, 118.2, 108.3, 105.7, 63.7, 62.5, 58.5, 45.7, 42.0, 26.9, 22.9, 19.6.

^1H NMR (400 MHz, $CDCl_3$): δ (representative signals for *epi*-**17g**) = 6.55 (m, 1 H), 6.05 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.30 (m, 1 H), 5.10 (s, 1 H), 3.94 (dd, *J* = 2.9 Hz, *J* = 11.7 Hz, 1 H), 3.72 (dd, *J* = 5.7 Hz, *J* = 11.7 Hz, 1 H), 2.26 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H).

Anal. Calcd for $C_{18}H_{24}N_2O$ (284.40): C, 76.02; H, 8.51; N, 9.85. Found: C, 76.16; H, 8.50; N, 9.83.

(1*R*)-1-Methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (21a); Typical Procedure
10% Pd/C (0.048 g) was added to a soln of **16a** (0.476 g, 1.9 mmol) in MeOH (10 mL) inside an autoclave and the mixture was kept under H_2 (7 bar) for 2 d. The catalyst was filtered off on a small pad of Celite and the organic soln was concentrated under vacuum. The oily residue was purified by column chromatography [SiO_2, CH_2Cl_2–MeOH (95:5)] to give an orange oil; yield: 0.205 g (81%); $[\alpha]_D^{20}$ +8.3 (*c* 0.7, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.54 (t, *J* = 2.4 Hz, 1 H), 6.15 (dd, *J* = 2.8 Hz, *J* = 3.6 Hz, 1 H), 5.90–5.80 (m, 1 H), 4.06 (q, *J* = 6.8 Hz, 1 H), 3.95–3.90 (m, 2 H), 3.38–3.31 (m, 1 H), 3.24–3.15 (m, 1 H), 1.06 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.9, 119.0, 107.7, 102.3, 49.5, 45.4, 43.4, 31.0.

MS (ES): *m/z* = 136.1 $[M + H]^+$.

Anal. Calcd for $C_8H_{12}N_2$ (136.19): C, 70.55; H, 8.88; N, 20.57. Found: C, 70.28; H, 8.91; N, 20.50.

(1*R*)-1-Ethyl-(1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (21b)
This was prepared from **16b** (0.156 g, 0.6 mmol) as described above.

Orange oil; yield: 0.156 g (79%); $[\alpha]_D^{20}$ +11.8 (*c* 0.7, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.55 (t, *J* = 2.1 Hz, 1 H), 6.15 (t, *J* = 3.4 Hz, 1 H), 5.90–5.88 (m, 1 H), 3.95–3.87 (m, 3 H), 3.38–3.35 (m, 1 H), 3.20–3.12 (m, 1 H), 2.03–1.94 (m, 1 H), 1.74–1.62 (m, 1 H), 1.06 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.5, 118.8, 107.5, 102.3, 55.0, 45.3, 42.9, 28.2, 10.2.

MS (ES): *m/z* = 151.1 $[M + H]^+$ (100).

Anal. Calcd for $C_9H_{14}N_2$ (150.22): C, 71.96; H, 9.39; N, 18.65. Found: C, 71.63; H, 9.43; N, 18.58.

X-ray Crystallographic Study of Oxazolopyrrolopyrazine 14

The X-ray intensity data for **14** were measured on a Bruker SMART Apex II diffractometer equipped with a CCD area detector and a graphite monochromated Mo-Kα radiation source (λ = 0.71073 Å). Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. For all crystals, a full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART[29] was used for collecting frames of data, indexing reflections, and determining lattice parameters. The collected frames were then processed for integration by SAINT[29] software, and an empirical absorption correction was applied with SADABS.[30] The structure was solved by direct methods (SIR 97)[31] and subsequent Fourier syntheses, and refined by full-matrix least-squares calculations on F^2 (SHELXTL),[32] attributing anisotropic thermal parameters to the nonhydrogen atoms. All hydrogen atoms were located in the Fourier map. The aromatic and methylene hydrogen atoms were placed in the calculated positions, refined with isotropic thermal parameters $U(H) = 1.2\ Ueq$(C), and allowed to ride on their carrier carbons, whereas the methine H atoms were located in the Fourier map and refined isotropically [U(H) = 1.2 U_{eq}(C)]. Crystal data and details of the data collection for **14** are reported in Table 3.

Table 3 Crystal Data and Structure Refinement for **14**

Compound	**14**
Formula	$C_{15}H_{16}N_2O$
M	240.30
T, K	296(2)
Crystal symmetry	monoclinic
Space group	$P2_1$
a (Å)	8.2411(4)
b (Å)	7.3720(4)
c (Å)	11.1066(6)
α (°)	90
β (°)	110.220(3)
γ (°)	90
V (Å^3)	633.18(6)
Z	2
D_c (Mg m^{-3})	1.260
μ(Mo-Kα) (mm^{-1})	0.080
F(000)	256
Crystal size (mm)	0.30 × 0.28 × 0.25
θ limits (°)	1.95–26.99
Reflections collected	9380
Unique obs. reflections [$F_o > 4\sigma(F_o)$]	2761 [R(int) = 0.0529]
Goodness-of-fit-on F^2	1.114
R_1 (F)[a], wR_2 (F^2)[b]	0.0436, 0.1008
Largest diff. peak and hole, e. (Å^{-3})	0.323 and -0.217

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.
[b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$ where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + F_c^2)/3$.

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(25) Crystallographic data for compound **14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 792774; copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].

(26) It is noteworthy that tricyclic tetrahydrooxazolopyrazolopyridine structures with three carbon stereocenters have been prepared as single diastereomers from 2-pyrrolecarboxaldehyde, (*S*)- or (*R*)-α-amino acid esters, and (+)- or (–)-norephedrine. The configuration of the newly formed stereocenter in the oxazolidine ring depends only on the chirality of the norephedrine. However, the potential of such compounds as precursors of chiral iminium ions, which could serve as suitable substrates for the addition of Grignard reagents, was not considered during the work reported here.

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